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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/735,296	01/14/2000	Shu-Hsia Chen	6923-084	7224

20583 7590 05/13/2005

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EXAMINER	
LI, QIAN JANICE	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 05/13/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/735,296	CHEN ET AL.	
	Examiner	Art Unit	
	Q. Janice Li	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 January 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *38,42,46,48,50,52,54,56,58,60,62,64,66,68,70 and 76-83* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *38,42,46,48,50,52,54,56,58,60,62,64,66,68,70 and 76-83* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *01 April 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1/27/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The amendment filed on 1/27/05 has been entered. Claims 56 and 60 have been amended. Claims 27, 72-75 have been canceled. Claims 76-83 are newly submitted. Claims 38, 42, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, and 76-83 are under current examination.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

ENABLEMENT REQUIREMENT

Claims 38, 42, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70 stand rejected and the rejection applies to new claims 76-81 for reasons of record and following.

Applicants argue that the specification and claims provide a variety of routes for administering the nucleic acid, and the literature provides numerous examples of IL-12 adenoviral vectors administered by routes other than intratumoral administration, such as intranasal (Worth) and intravenous (Siders). Applicants further submitted new references Kim for systemic, and Etgen for intramuscular administration.

In reply, the rational for *Siders* administering the adenovirus intravenously has been discussed previously (page 4 of the action mailed 7/19/04), thus will not be reiterated here. The intranasal administration taught by *Worth et al* and intramuscular

administration taught by *Etgen et al* are considered as topical administration because the target tissue in *Worth* and *Etgen* were lung and muscle tissue, respectively. As to *Kim et al* (IDS/C04), they teach treating arthritis, not cancer, which is a much more difficult task due to the aggressive nature of tumor cells. *Kim et al* induced experimental arthritis by systemic intradermal (collagens) and intraperitoneal (LPS) route, and thus using *both* local and systemic adenovirus-mediated delivery of IL-4, the therapeutic effect was obtained primarily by localized administration. The systemic delivery only postponed onset or reduced severity in early stage arthritis. Moreover, in an unpredictable art such as gene therapy, the enablement of the claimed invention is evaluated on a case-by-case basis. After all, "LAW REQUIRES THAT THE DISCLOSURE IN APPLICATION SHALL INFORM THOSE SKILLED IN THE ART HOW TO USE APPLICANT'S ALLEGED DISCOVERY, NOT HOW TO FIND OUT HOW TO USE IT FOR THEMSELVES" *In re Gardner* 166 USPQ 138 (CCPA) 1970. Thus, the submitted references are insufficient to support the full scope of the instant claims.

Applicants go on to argue that various vectors are known in the art, and assert that one would be able to choose an appropriate vector even though that some embodiment may not work.

In response, it is noted all of the references cited by the Office or submitted by applicants were drawn to using adenoviral vectors. Applicants are again reminded that 35 U.S.C. § 112 requires that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art. *In re Fisher*, 166 USPQ 18, 24 (CCPA 1970). . It is the

specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement. *Genentech Inc. v. Novo Nordisk A/S,* 42 USPQ2d 1005 (CAFC 1997)

Accordingly, for reasons of record and those set forth *supra*, the specification fails to provide an enabling disclosure to support the full scope of the invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 38, 42, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 70 stand rejected and claims 76-82 are newly rejected under 35 U.S.C. 103(a) as being unpatentable over *Caruso et al* (PNAS 1996;93:11302-6), taken with *Melero et al* (Nat Med 1997;3:682-5, IDS/CA), and *Kim et al* (Eur J Immunol 1998;28:881-90, IDS/DM).

Applicants first argue that there is no motivation to combine the cited references.

In response, the motivation for combining various means for cancer therapy was clearly suggested by *Caruso et al*, who teach because of the currently available cancer treatment modalities are far from ideal, "THE DEVELOPMENT OF ALTERNATIVE TREATMENTS FOR METASTASES OF COLON CANCER IS NEEDED TO IMPROVE THE CLINICAL OUTCOME OF PATIENTS" (1st paragraph, page 11302). *Caruso et al* go on to teach combining multiple means for metastasis cancer, such as combined suicide (tk) and IL-2 gene therapy (page 11303),

and further combining IL-12 treatment with IL-2/tk therapy. *Caruso et al* teach, "THIS ADDITIONAL TREATMENT CAN POTENTIALLY ENHANCE THE ANTITUMORAL EFFICACY OF IL-12 AND INDUCE A LONG-LASTING SYSTEMIC ANTITUMORAL IMMUNITY" (last paragraph, page 11305). Applicants are reminded that the test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference; nor is it that the claimed invention must be expressly suggested in any one or all of the references. Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981). Since *Caruso et al* clearly suggested and practiced the combined cancer therapy, it is a clear indication that one would have motivated to combine the proven effective therapeutic means for treating cancer with a reasonable expectation of success.

Applicants then disagreed with the Examiner's position that one would expect that IL-12 and 4-1BBL act synergistically because of a common shared mechanism, i.e. enhancement of Th1 response and IFN-γ production. Applicants asserted the prior art did not teach these mechanisms were responsible for the roles of IL-12 and 4-1BBL, and simply pointed to Worth et al and Siders et al as support without details.

In response, as an initial matter, the instant rejection is not relied on *Worth* and *Siders* references. The commonly shared mechanisms of IL-12 and 4-1BBL have been taught by both *Caruso et al* and *Kim et al,* and cited in the previous Office action (page 7). With respect to *Worth et al*, who stated that the mechanism of IL-12 is not *fully* understood because there may be many mechanisms involved, including T cell-

dependent and T cell-independent pathways. Unlike *Caruso* or *Melero, Worth et al* used an immunodeficient animal model, which lacks both CD4+ and CD8+ T cells, and thus the role of these T cells could not have been studied in such a model. Nevertheless, *Worth et al* confirmed that IL-12 did activated NK cells and increased IFN-γ production in their model (page 3717, 3rd paragraph). This further supported the teaching of *Caruso et al* as cited previously. With respect to *Siders*, similar observation were taught as reported by *Worth et al* since they both used a nude mice model, i.e. NK cells and IFN-γ were involved in the antitumor effects of IL-12 (2nd paragraph, page 5472).

Applicants go on to argue that *Melero* does not show anti-tumor effect without artificially enhancing 4-1BB on tumor cells, and *Kim* merely discusses CD28 and 4-1BB co-stimulation in promoting Th1 cell responses, but does not demonstrate an anti-tumor effect at all.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). In the instant case, the anti-tumor effects were taught by *Melero et al,* and *Kim et al* supplemented the teachings of *Melero et al* by further showing it is well known in the art how 4-1BB works. Here, *Kim et al* not only taught the involvement of Th1 response but also the benefit to combining 4-1BB signal with other means of treatment.

Additionally, the court has determined that finding obviousness does not require expressly written motivation to combine in prior art since the motivation to combine may

be found in the nature of the problem to be solved. "FINDING OF OBVIOUSNESS DOES NOT REQUIRE EXISTENCE OF EXPRESS, WRITTEN MOTIVATION TO COMBINE IN PRIOR ART, SINCE MOTIVATION TO COMBINE MAY BE FOUND IN NATURE OF PROBLEM TO BE SOLVED, LEADING INVENTORS TO LOOK TO REFERENCES RELATING TO POSSIBLE SOLUTIONS TO THAT PROBLEM". (*Ruiz v. A.B. Chance Co.*, 69 USPQ2d 1686 CA FC 2004). Also, "FINDING OF MOTIVATION TO COMBINE PRIOR ART REFERENCES NEED NOT BE SUPPORTED BY SHOWING THAT CLAIMED COMBINATION IS PREFERRED OVER OTHER ALTERNATIVES, SINCE PROPER INQUIRY IS WHETHER THERE IS SOMETHING IN PRIOR ART AS WHOLE TO SUGGEST DESIRABILITY, AND THUS OBVIOUSNESS, OF MAKING COMBINATION, NOT WHETHER THERE IS SOMETHING IN PRIOR ART AS WHOLE TO SUGGEST THAT COMBINATION IS PREFERRED OR MOST DESIRABLE. (*In re Fulton*, 73 USPQ2d 1141 CA FC 2004) Here, both *Caruso et al* and *Melero et al* teach solving a problem in treating tumor and the need for combined cancer therapy. Thus it would have suggested to the skilled artisan to look to references relating to possible solutions. Whether IL-12 and 4-1BBL act through the same or different mechanism should not affect the desirability to combine because they could either supplement or complement each other via the same or different pathways.

With regard to teachings of *Melero et al,* it is unclear where in *Melero* they teach artificially enhance 4-1BB on tumor cells. *Melero et al* do teach that the anti-4-1BB antibody (4-1BBL) did not induce antitumor T cell response in *non*-tumor-bearing mice but induced potent T-cell response in tumor-bearing mice, even the large tumors of poor immunogenicity (e.g. page 684). This teaching enforces the desirability to use 4-1BBL for cancer therapy.

Applicants then argue that the Examiner has not demonstrated the prior art teachings that IL-12 and 4-1BBL would enhance the T cell response and IFN-γ production in a synergistic manner. Applicants also argue the combination of Hirschowitz and Kim.

Applicants are reminded that *Hirschowitz* is not relied as the bases of this rejection. The rational for a reasonable expectation of a synergistic effect have been set forth on record and *supra*. Moreover, Note that obviousness does not require absolute predictability of success; for obviousness under 35 U.S.C. § 103, all that is required is a reasonable expectation of success. See In re O'Farrell, 7 USPQ2d 1673 (CAFC 1988).

Accordingly, for reasons of record and set forth *supra*, the rejection stands.

Claim 83 is newly rejected under 35 U.S.C. 103(a) as being unpatentable over *Caruso et al* (PNAS 1996;93:11302-6), taken with *Melero et al* (Nat Med 1997;3:682-5, IDS/CA), and *Kim et al* (Eur J Immunol 1998;28:881-90, IDS/DM), as applied to Claims 38, 42, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 70, 76-82 above, and further in view of *Hirschowitz et al* (Gene Ther 1998;5:975-83).

The combined teachings of *Caruso et al* in view of *Melero et al* and *Kim et al* fail to teach intranasal administration as required by claim 83. *Hirschowitz et al* supplemented the combined teachings by illustrating that it is well known in the art administering a therapeutic adenoviral vector via intranasal route for treating lung cancer.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the methods taught by *Caruso et al* in view of *Melero et al* and *Kim et al* by using the intranasal route as taught by *Hirschowitz et al* for treating lung cancer with a reasonable expectation of success. Given the success as taught by *Hirschowitz et al,* the skilled would have had a reasonable expectation of success using the intranasal route for delivering AdvIL-12. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Q. Janice Li** whose telephone number is 571-272-0730. The examiner can normally be reached on 9:30 am - 7 p.m., Monday through Friday, except every other Wednesday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Ram R. Shukla** can be reached on 571-272-0735. The fax numbers for the organization where this application or proceeding is assigned are **571-273-8300**.

Any inquiry of formal matters can be directed to the patent analyst, **Dianiece Jacobs**, whose telephone number is (571) 272-0532.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system

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Q. JANICE LI, M.D.
PRIMARY EXAMINER

Q. Janice Li
Primary Examiner
Art Unit 1632

QJL
May 9, 2005